at

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL

Tuesday, September 10, 2002

8:00 a.m.

Hilton Washington D.C. North
620 Perry Parkway
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
735 8th Street, S.E.
Washington, D.C. 20003-2802
(202) 546-6666

PARTICIPANTS

Cynthia M. Tracy, M.D., Chair
Elisa Harvey, D.V.M., Interim Executive Secretary
Geretta Wood, Executive Secretary

Voting Members
Salim Aziz, M.D.
Warren K. Laskey, M.D.

Consultants
Kent R. Bailey, Ph.D.
Kyra J. Becker, M.D.
Blase A. Carabello, M.D.
Anthony Comerota, M.D.
Ronald M. Lazar, Ph.D.
John R. Marler, M.D.
Michael J. Pentecost, M.D.
Ileana L. Pina, M.D.
George W. Vetrovec, M.D.
Christopher J. White, M.D.
Justin A. Zivin, M.D., Ph.D.

Consumer Representative
Robert A. Dacey

Industry Representative
Michael C. Morton

FDA
Bram Zuckerman, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. TRACY: Good morning. We will go ahead and call this morning's session to order This is the Circulatory Systems Device Panel. Today' topic is the discussion of a premarket application, NMT Medical Septal Occlusion System.

DR. HARVEY: I would like to read the conflict-of-interest statement. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict-of-interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interest. The agency has determined, however, that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

We would like to note for the record that the agency took into consideration matters regarding Drs. George Vetrovec and Kyra Jo Becker. These panelists reported interests in firms at issue but in matters that are not related to today's agency. Therefore, the agency has determined that these individuals may participate fully in all discussions.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. TRACY: Thank you.

Can I ask the members of the panel to introduce themselves, please.

MR. MORTON: I am Michael Morton. I am with Soren Coe Cardiovascular(?). I am the industry representative.

DR. AZIZ: Salim Aziz, adult cardiac surgery from Denver, Colorado.

DR. COMEROTA: Anthony Comerota, vascular surgeon from the Jobst Vascular Center in Toledo and University of Michigan, Ann Arbor.

DR. PINA: Ileana Pina, Director of Heart Failure Transplant, Case Western Reserve University, Cleveland.

DR. VETROVEC: George Vetrovec, Chief of Cardiology, Medical College of Virginia Campus, Virginia Commonwealth University in Richmond.

DR. WHITE: Chris White, interventional cardiologist for the Ochsner Clinic in New Orleans, Louisiana.

DR. PENTECOST: Michael Pentecost. I am Professor and Chairman of Radiology at Georgetown.

MS. WOOD: Geretta Wood, Executive Secretary.

DR. HARVEY: Elisa Harvey, Interim Executive Secretary for this meeting.

DR. TRACY: I am Cindy Tracy. I am the Interim Chief of Cardiology at Georgetown University Hospital. I am an electrophysiologist.

DR. BECKER: Kyra Becker, University of Washington.

DR. LASKEY: Warren Laskey, interventional cardiologist from Baltimore.

DR. BAILEY: Kent Bailey. I am a biostatistician at Mayo Clinic.

DR. ZIVIN: Justin Zivin, neurosciences, University of California, San Diego.

DR. LAZAR: Ronald Lazar, neuropsychologist, Columbia Presbyterian Medical Center, New York.

DR. CARABELLO: I am Blase Carabello, cardiologist and Chief of Medicine at the Houston V.A.

MR. DACEY: Robert Dacey, consumer representative, Boulder County, Colorado.

DR. ZUCKERMAN: Bram Zuckerman, Director, Division of Cardiovascular Devices, FDA.

DR. HARVEY: I would like to read the voting-status statement. I have appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990 and as amended August 18, 1999, I appoint the following individuals as voting members of the Circulatory System Devices Panel for this meeting on September 10, 2002; Anthony Comerota, Christopher White,

Michael Pentecost, George Vetrovec, Kent Bailey, Kyra Becker, Ronald Lazar and John Marler.

For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict-of-interest review and have reviewed the material to be considered at this meeting.

It is signed by David Feigel, the Director of the Center for Devices and Radiological Health dated August 30, 2002.

I have a second appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990 and as amended August 18, 1999, I appoint the following individuals as voting members of the Circulatory System Devices Panel for the meeting on September 10, 2002: Blase Carabello, Ileana Pina and Justin Zivin.

For the record, Dr. Carabello is a voting member and Dr. Pina is a consultant to the Cardiovascular and Renal Drugs Advisory Committee of the Center for Drug Evaluation and Research.

Dr. Zivin is a consultant to the Center's Peripheral and Central Nervous System Drugs Advisory Committee. They are special government employees who have undergone the customary conflict-of-interest review and have reviewed the material to be considered at this meeting.

It is signed by William Hubbard, Senior Associate Commissioner for Policy and Planning on behalf of Linda Skladany, the Senior Associate Commissioner for External Relations, dated September 2, 2002.

DR. TRACY: At this point, I will open up the Open Public Hearing.

Open Public Hearing

DR. TRACY: There were no scheduled speakers, but if there is anybody who would care to speak, please identify yourself at the microphone.

If not, we will close the open public hearing and move on to the sponsor's presentation.

Sponsor Presentation: NMT Medical

P000049/S3, CardioSEAL STARFlex

Septal Occlusion System with Qwik Loader

DR. HARVEY: I would remind the sponsors that they should please, first of all, use the mike for every time that you are speaking to the panel,

introduce yourself when you begin to speak and also state your conflict of interest.

Thank you. You can start.

Introduction and Opening Remarks

MR. AHEARN: Good morning.

[Slide.]

My name is John Ahern. I am an employee and shareholder of NMT Medical. I am also the President and Chief Executive Officer.

[Slide.]

NMT Medical is located in Boston. We have 100 employees and we have been in the cardiovascular implant business for the last sixteen years. We are before this advisory panel today to review a PMA supplement submitted to the FDA in April for the percutaneous closure of patent foramenal valley in a very select group of patients having a high risk of embolic stroke.

I would like to thank the staff at the FDA, the panel chair and the panel members for their time and consideration today.

[Slide.]

You will hear from four additional speakers covering the following areas; the percutaneous closure for PFO, the PFO closure

device description, clinical-trial overview analysis and outcomes, and concluding remarks.

[Slide.]

Speaking on behalf, or from, NMT Medical will be Michael Landzberg. Dr. Landzberg is a cardiologist and Director of the Boston Adult Congenital Heart and Pulmonary Hypertensive Services at Brigham and Women's Hospital and Children's Hospital, Boston.

Carol Ryan; Ms. Ryan is Vice President of Research and Development for NMT Medical. Kathy Jenkins: Dr. Jenkins is a cardiologist and Assistant Professor of Pediatrics at Harvard Medical School, an Associate in Cardiology at Children's Hospital, Boston. Nancy Futrell: Dr. Futrell is a neurologist and is Chair of the Stroke Section of the American Academy of Neurology and the Director of the Intermountain Stroke Center, Salt Lake City.

[Slide.]

We also have invited experts to help answer the advisory panel's questions during the discussion portion of the meeting. With us today are: Peter Block, cardiologist; Amy Britt, clinical researcher; Ferdinando Buanonno, neurologist;

Kimberlee Gauvreau, biostatistician; Kathryn Hassell, hemotologist; Thomas Hougen, cardiologist and also Chair of the Safety Committee for this high-risk study.

[Slide.]

Richard Kuntz, cardiologist; William Likosky, neurologist; Igor Palacios, cardiologist; Mark Reisman, cardiologist; and Carole Thomas, neurologist.

[Slide.]

Worldwide, over 8,000 successful percutaneous-closure procedures of the patent foramenal valley have been completed in stroke patients using the company's CardioSEAL and STARFlex technology. Several thousand more patients have benefited from percutaneous closure of atrial septal and ventricular septal defects.

The company's devices for percutaneous closure of cardiac septal defects have been commercially available outside the United States for over six years.

In February of 2000, the FDA gave the company HDE approval for our CardioSEAL device for percutaneous closure of patent foramenal valley in patients with recurrent stroke that have failed

medical therapy. This HDE approval and the patients treated under the HDE has established the safety and probable benefit of percutaneous closure of PFO in select patients.

Currently, over 150 institutions in the United States have IRB approval for HDE access for this device procedure and indication. In December of 2001, the FDA granted PMA approval for the same device for percutaneous closure of ventricular septal defects in certain high-risk patients.

The data we are presenting today is derived from the same multicenter study that was the basis for PMA approval given less than a year ago. Published reports in peer-review journals including the latest issue of Circulation suggest that the company's percutaneous closure devices are effective and have low complication rates.

[Slide.]

Today, we are not seeking approval for a broad-based PFO indication. Additional studies are needed before this can happen. We are committed to fund and complete these larger studies. Today, we are seeking approval and agreement to expand the current PMA approval and indication to include percutaneous closure of patent foramenal valley in

a select group of high-risk patients using our latest generation STARFlex device.

A PMA approval would make treatment access less burdensome and less expensive than what is now required under HDE guidelines and, more importantly, a PMA approval would provide access to a next-generation device with a higher closure success rate.

We believe the study results before you offer reasonable assurance of safety and efficacy in this high-risk group of patients. We understand there are concerns about percutaneous closure for PFO stroke patients beyond the restricted PMA we are seeking. The company is very sensitive to that issue.

NMT Medical has a high level of experience working within restricted FDA HDE and PMA guidelines. Over the last few years, the company has operated under three different and separate HDE approvals. We have performed responsibly under these restricted approvals.

For the last year, we have worked within a very restricted PMA for VSD closure with the same device available under the three HDEs. We have performed responsibly under the restricted PMA.

Should we gain your approval today, we are fully committed to continue to perform responsibly. We have the systems in place and the experience to work under restricted PMA guidelines.

There is a slight change in the order of the agenda. I would now like to introduce Michael Landzberg who will take us through the description of the STARFlex implantation procedure.

Thank you for your attention.

Procedural Overview

DR. LANDZBERG: Thank you, John.

Good morning.

[Slide.]

My name is Michael Landzberg. For the past decade and change, I have directed the Boston Adult Congenital Heart Group between the Brigham and Women's Hospital and Children's Hospital in Boston. There I have performed the majority of interventional procedures in adults with congenital heart disease and, more specifically, with the collaboration of the neurologists, have participated in the majority of PFO closures when appropriate in an attempt to better understand and to effect some change in stroke prevention and recurrence.

I should add that I have no financial holdings with NMT Medical. They are covering the costs of my being here today.

[Slide.]

The task that I have been appointed is to discuss with you the technical aspects of STARFlex PFL closure. I intend to do that in three steps, as you see there. I will begin with a general animation describing PFO STARFlex closure. This will be followed by a more specific review of the requisite tools and the individual procedures associated with PFO closure and I will close by showing you an actual implementation under trans-esophageal echocardiography.

[Animation Slide.]

If you look up at the screen, after sedation, an individualized pain control access, venous access, obtained typically via the right femoral vein. An entry catheter is placed within the inferior vena cava of the right atrium across the foramenal valley into the left atrium and there a guidewire, as you see there, is place within the left atrium and, typically, within the left pulmonary veins and the entry catheter is removed.

A highly compliant balloon is placed

within the foramenal valley. This highly compliant balloon, itself, is distorted during inflation allowing a mimicry of the foramenal-valley anatomy so that the interventionalist can choose the appropriate size device for PFO closure.

At this point in time, I typically place, right here within the foramen, a pigtail angiographic catheter and inject 10 ccs of contrast getting a picture very similar to the one that you see here confirming the anatomy of the foramen and the appropriate choice of device size for closure.

Next, a 75 centimeter long 10 French sheath is introduced into the left atrium over the guidewire and the guidewire and the sheath dilator are removed. The appropriate STARFlex device is attached to a delivery catheter. This catheter is brought right here to the very distal end of the sheath where either the distal left atrial arms of the device are extruded into the left atrium or, more typically, the guiding sheath is retracted allowing delivery of those left atrial arms, as you will see here.

After confirmation of the arm positions, the combination sheath and delivery catheter are

retracted so that the left atrial arms are flush against the left atrial surface. At that point, the delivery sheath is further retracted allowing the right atrial arms to be delivered and, after appropriate confirmation of the device arm positioning, the catheter is removed from the device.

At s point, I would like to emphasize what you see here. What is occurring at this point for the clinician is a relatively silent but critically important adaptation and achievement of the STARFlex device and an improvement compared to the prior devices.

Technically, up until this point, the individual aspects of foramen closure are relatively basic for the interventional cardiologist. All foramen-occlusion devices accomplish their goal by retracting what you see here, the top and bottom portions of the foramenal valley against each other and allowing for some septal distortion inside the device, itself.

It is absolutely, for the interventional cardiologist, him or herself, impossible to personally manipulate the delivery system to achieve absolute maximal centering of the device

and minimal infolding and retraction inside the device, itself.

All prior foramen-occlusion devices had this same inability to maximally center the device and had more severe septal distortion, as you see here, and failed to allow for maximal complete closure of the foramenal valley.

That STARFlex system, itself, as you see here emphasized, has its own internal auto-adjusting spring mechanism which literally drives the device towards the anatomic center of the foramen allowing for less severe septal distortion and a more complete closure.

After the device has seated itself, the sheaths and catheters are removed from the patient. The patient is allowed to convalesce, typically within twenty-four hours is allowed to return home and, over the first few weeks, if not months, complete endothelialization has occurred and incorporation into the left atrial and right atrial surfaces of the septum have occurred.

[Slide.]

Most of the tools required for STARFlex PFO closure are those familiar in presence and use to the adult interventional cardiologist and

include standard wires, sheaths and catheters, as you see.

The sizing balloons and delivery sheaths that are specific to STARFlex PFO closure are very similar to those used in routine adult interventional procedures. Similarly, the STARFlex delivery catheters and devices may be novel to the adult interventionalist. However, their uses are exactly similar to very standard coronary interventions and their novelty is relatively short-lived.

[Slide.]

I am going to review with you the individual steps involved with PFO closure as seen during a cardiac catheterization, a little bit more specific than the animation you saw before.

[Animation Slide.]

After sedation and analgesia, from the inferior vena cava into the right atrium, into the left atrium, a catheter is placed and it is anchored here in the left pulmonary. I have injected, once you see, a contrast to confirm positioning. I leave a guidewire in this position, remove that initial catheter.

[Animation Slide.]

You see here an angiographic catheter placed within the foramen defining the anatomy for appropriate choice of STARFlex sizing for implantation.

[Animation Slide.]

A balloon catheter is placed directly within the foramen, as you see here, confirming the anatomy and the appropriate choice of STARFlex for implantation.

[Animation Slide.]

A 75-centimeter long sheath is implanted into the left atrium and the STARFlex device is now attached to a delivery system and placed within this guide sheath.

[Animation Slide.]

It is at the very tip of the guiding sheath and I have retracted the sheath allowing the distal-most arms to be delivered into the left atrium, as you see.

[Animation Slide.]

Both the delivery catheter and sheath are retracted so that the arms are flush against the atrial septum and device-arm positioning is confirmed here with trans-esophageal echo cardiography. But this can be confirmed either

fluoroscopically or the intracardiac echo.

[Animation Slide.]

Once those arms are confirmed to be in appropriate position, the sheath is further retracted, the right atrial arms are delivered.

[Animation Slide.]

Again, arm positioning is confirmed either fluoroscopically or with the assistance of echocardiography.

[Animation Slide.]

At that point, the device is released from the delivery catheter.

[Animation Slide.]

Right atrial angiography may be performed to confirm appropriate device positioning.

[Slide.]

As you see here, in this still frame, the device can be shown to be perfectly locking to foramen closed.

[Slide.]

I would like to end with a final recapitulation. You will see an actual implantation of a STARFlex device via trans-esophageal echo cardiography.

[Animation Slide.]

Let me review with you very quickly. This is the right atrium, this empty space here. The left atrium here between the two is the atrial septum and the foramenal-valley color is used to represent velocity of blood flow. You will see flow within the foramenal valley, itself, here.

After sedation, again, as you recall, a catheter is used to cross the foramenal valley. A guidewire is implanted in that position and, over that guidewire, is place a highly compliant balloon which you will see inflated in a second.

That dilation balloon will, in fact, mimic the anatomy of the atrial septum allowing for the implanter to determine the absolute size of an implantation STARFlex device. You will see the distortion of that balloon occurring now.

Once that has been accomplished, the angiographic balloon is removed. I place an angiographic catheter there to define the anatomy again and a long sheath is placed over the guidewire. Through that sheath is placed the delivery device and catheter system to the very end of the delivery sheath.

At that point, the sheath is retracted allowing the distal left atrial arms to be deployed

and you will see that occurring here. From this moment on, the internal auto-adjusting springs of the STARFlex device literally drive this catheter and device system towards the anatomic center of the foramen allowing it to achieve minimal septal distortion.

This process usually takes about a minute as we retract the entire system confirming the arm positioning until they are flush against the left atrial surface here of the foramenal valley. Once that has been confirmed, the catheter is further retracted allowing the right atrial arms to be deployed, and you will see that momentarily.

As the right atrial arms are deployed, further confirmation of their positioning is obtained either fluoroscopically or with the use of echocardiography, as you see here, and the device is released from the delivery catheter. It assumes its more normal position.

At that point, the sheaths, catheters, are removed from the body. The patient is allowed to convalesce after hemostasis is achieved. The patient returns home typically within a twenty-four hour period of time.

I think you for your attention..

At this point, I would like to introduce Carol Ryan who is the Vice President for Research and Development for NMT Medical.

Device Description

MS. RYAN: Good morning.

[Slide.]

My name is Carol Ryan. I am an NMT employee and a shareholder.

[Slide.]

The STARFlex device has been designed for percutaneous closure of intracardiac defects. It is delivered using the PMA-approved CardioSEAL delivery system and is a third-generation device which is a modification of the CardioSEAL.

[Slide.]

The CardioSEAL is a redesign of the Clamshell. The framework was changed and the design changed to improve fatigue and corrosion resistance. The STARFlex is a modification of the CardioSEAL. A centering mechanism was added to improve centering and reduce the residual leak rate. They are similar in that the tissue scaffold is the same and, histopathologically, they have had the same results.

[Slide.]

The STARFlex is available in three sizes, 23, 28 and 33 millimeter. It is fabricated from MP35n. There are radiopaque markers at the distal tip of each arm. Polyester fabric is the tissue scaffold and polyester suture is used to attach it. There is a pin-attachment mechanism for attachment to the delivery system.

[Slide.]

The only difference between STARFlex and CardioSEAL is the nitinol centering spring. The advantages of STARFlex are the improved device centering and better apposition of device arms to the septal wall. This results in significant changes, both a lower septal profile and higher complete closure rates.

[Slide.]

The STARFlex implant is attached and packaged with the Qwik Loader using nylon suture and a loader button. The Quik Loader is used to collapse the implant and introduce it into the sheath and it is identical to the PMA-approved CardioSEAL Quik Loader.

[Slide.]

The critical STARFlex design features are that it is designed for long-term biocompatability,

it utilizes a well-characterized tissue scaffold which encourages fast and thorough tissue encapsulation as you can see here in this sheath explant at 90 days with both the fabric and the device arms are fully endothelialized.

It has excellent corrosion resistance, a low metal surface area, is conformable to a variety of anatomies and has a low profile in the septum to minimize hemodynamic disturbances. Additionally, it is MRI compatible.

Next I would like to introduce Dr. Kathy Jenkins from the Department of Cardiology at Children's Hospital, Boston. Dr. Jenkins will talk about the clinical-trial overview.

Clinical Trial Overview

DR. JENKINS: Thank you. Good morning.

[Slide.]

My name is Kathy Jenkins. I am actually going to give this presentation as well as the following one on behalf of my colleague, Dr. Kimberlee Gauvreau who is not available today but will be available by telephone conference for questions after 10:15.

My institution, the Children's Hospital in Boston, has a licensing agreement with NMT Medical

for the STARFlex technology based on the Chairman of Cardiology, Jim Locke's, original contribution to the original invention. In addition, this study was not originally funded by NMT Medical Technology. The data for the presentation was obtained by NMT from Children's Hospital under a separate licensing agreement.

Both Dr. Gauvreau and I were assigned as some of the intellectual property associated with the data agreement but the majority is held by our employer, the Boston Children's Heart Foundation. Also, my time and expenses are being paid for me to be here with you today.

I am a pediatric cardiologist and clinical researcher at Children's Hospital and the principal investigator for this study.

[Slide.]

What I would like to do is summarize for you the information that has been presented in the panel packet. As I am sure you are aware, it is a complex submission consisting of four cohorts of patients. Three of these are PFO cohorts for each of the three generations of the STARFlex device.

The pivotal cohort is from the STARFlex, itself. Two other cohorts from the predecessor

devices, the CardioSEAL and Clamshell I devices, are also shown, as well, an additional cohort of STARFlex devices implanted in non-PFO patients.

[Slide.]

This data is from a study that is a prospective, multicenter trial that is ongoing and began enrollment in May of 1996. Currently, there are over 650 patients enrolled in this study and enrollment through September 1, 2001 was submitted for the purposes of the PMA. Children's Hospital in Boston is the sponsor of the study.

The study is overseen by a safety and data monitoring committee. The study includes patients with patent foramenal valley as well as other types of defects and data from this specific study were used to support PMA approval for VSD as well as the three HDE approvals NMT was granted for the CardioSEAL technology.

[Slide.]

This high-risk study was designed to evaluate the safety and efficacy of the STARFlex device in patients with limited acceptable alternatives. It is a prospective cohort of implanted patients without a control group.

[Slide.]

The referral and entry process for the study is shown in this slide. Patients were referred to the implanting centers by, in the case of PFO, their neurologists or other treating physicians. The information is then reviewed by an interventional cardiologist to determine suitability for moving forward.

The information about the patient was then presented to an independent peer-review team of an uninvolved cardiologist and cardiac surgeon who determined that the information provided was complete and determined the final entry of patients into the study. This same process was used for non-PFO indication.

[Slide.]

The criteria used by the peer-review team were that the patient had one or more cardiac defects that resulted in sufficient hemodynamic derangement to warrant intervention with either a type of defect that is technically difficult or impossible to close surgically or an overall medical condition such that the surgical risks are sufficient to justify the known and potential unknown risks of the device-closure procedure.

[Slide.]

Throughout the remainder of the study, the management of patients was primarily dictated by their treating physician. However, the outcome evaluations were performed according to the study protocol and baseline discharge 1, 6, 12 and 24 months following implantation.

These assessments included a clinical evaluation, chest X-ray, EKG, echocardiogram and fluoroscopy at 6 and 24 months. Core laboratories were responsible for the final interpretation of chest X-rays and fluoroscopies as well as echocardiograms.

[Slide.]

In terms of presenting the efficacy information for this submission, we outlined the following goal of treatment. The primary goal of treatment for this procedure in this cohort was to alter the negative health state associated with PFO patency where the negative health state resulted in right-to-left shunting or risk for systemic emboli.

[Slide.]

Based on that goal, the primary outcome for this submission is PFO eradication. Secondary outcomes were improvement in oxygen saturation in cyanotic patients as well as the occurrence of

embolic events.

[Slide.]

The primary efficacy outcome or PFO closure status was defined in the protocol to be by echocardiography. The use of trans-esophageal echocardiograms and contrast injections were specifically left to the discretion of treating physicians at a specific meeting where this was discussed by the Safety Committee on June 12, 1998.

The committee recommended trans-esophageal echocardiograms if trans-thoracic views were deemed inadequate and also recommended that a contrast injection be performed at at least one follow-up time point in all PFO patients.

[Slide.]

This slide shows the residual flow categories by which closure status was determined. Absent meant no detectable color flow or a negative contrast injection. Trivial was less than a 1-millimeter jet. Small, less than up to 3 in adults and more than small greater than that.

Once again, I should emphasize that these were reviewed by a core laboratory.

[Slide.]

Improvement in oxygen saturation was

judged as a change from preimplantation baseline and cutaneous oxygen saturation at discharge six months post-implantation and most recent follow up.

[Slide.]

The occurrence of embolic events was ascertained at each follow-up time point but are presented to you throughout the entire period of follow up. The evaluation and management decisions about these events were made by the treating physician but all of the events were reviewed by the Safety and Data Monitoring Committee.

[Slide.]

We retrospectively categorized potential embolic events for the purpose of this submission using the following definitions: CVAs or strokes with permanent neurological deficits or lesions seen on imaging studies; classic TIAs as classic face and arm weakness and speech impairment; in middle cerebral-artery distribution with complete recovery by 24 hours after onset, and no permanent deficits on imaging; transient visual symptoms and other transient events.

[Slide.]

In terms of the safety assessment for the product, we used a comprehensive definition similar

to drug studies whereby all adverse events occurring at any time point during follow up were recorded. Each of these events was independently reviewed by a safety and data monitoring committee who were responsible for the final data classification in terms of attributability and seriousness.

[Slide.]

These are the degree-of-seriousness categories that were used by the safety committee using a standard definition.

[Slide.]

As well as the attributability categories. We used three categories of attributability, definitely, probably or possibly where possibly was plausibly, similar to drug studies, related to device positioning, device arm fracture, otherwise to device, specifically to the implant portion of the catheterization or to the catheterization, itself or a variety of unrelated categories.

[Slide.]

The primary safety outcome was descriptive, defined as the proportion of patients with at least one serious or moderately serious event that was probably or definitely related to

the device implant or catheterization procedure.

[Slide.]

A more comprehensive definition of all events that occurred during follow up was a secondary safety outcome.

[Slide.]

Just to remind you that we also have presented information about a CardioSEAL cohort. These patients were derived from the exact same trial as the STARFlex cohort using identical methodology.

[Slide.]

A Clamshell I cohort is derived from a different source. This information is from a retrospective registry of all patients implanted at Children's Hospital with devices during the original Clamshell regulatory trials. Our database was retrospectively created in 1994 at the time of the Clamshell I FDA audits and then has been followed prospective since then.

It also includes patients with patent foramenal valley as well as other types of defects and is primarily intended as a screen for late device-related and other major clinical events.

[Slide.]

As it is a registry, follow-up testing is recommended by not required. It becomes more frequent at later time points after implant.

[Slide.]

In terms of adverse events that have recorded since 1994, neurological events have been specifically screened for evaluating the clinical data that has been obtained.

[Slide.]

Echo closure status is defined similarly, although there is not a distinction in this group between trivial and absent defects.

Trial Analyses, Results and Conclusions

DR. JENKINS: I would now like to show you the results from the study.

[Slide.]

This information, as I said, was prepared by my colleague, Dr. Kimberlee Gauvreau.

[Slide.]

The PFO pivotal cohort contains information about 49 patients who had a STARFlex device implanted to close a PFO. All of these patients had the device successfully implanted at a single procedure with a single device.

[Slide.]

Although the entry criteria for our study was judgment based, for the purposes of clarification of the data presented to you, we have outlined the indications for enrollment for you on this slide. As you can see, it was fairly diverse. Patients had both complex and medical disease or both, hypercoagulable states, right-to-left shunting as a primary indication, failures of medical therapy and, as you can see at the bottom, somewhere in the range of 25 to 30 percent of the cohort had nonmedical contraindications to medical therapy.

Interestingly, the peer reviewers often cited the occurrence of the stroke as the reason for entry into the study as a contraindication to surgery.

[Slide.]

Thirty-nine patients had a prior neurological event as the primary reason that they were referred for closure. Seven patients had right-to-left shunting as the primary reason and three patients had both.

You can see the age distribution of the patients who were enrolled. I should say that these procedures were all performed at pediatric

institutions so, for us, this is a rather old cohort. The majority of the patients were between twenty and fifty years of age.

[Slide.]

All of the three available sizes of STARFlex are represented in this dataset.

[Slide.]

The use of medications pre- and post-device placement were dictated by treating physicians based on individual patient indications. Aspirin is recommended for six months after implant as a part of our study design.

[Slide.]

As you can see in this slide, the use of medicines was variable but did shift after device placement with nearly half the cohort on no anticoagulation after six months and a substantially fewer number of patients on Coumadin at that period.

[Slide.]

This slide now shows the data for the primary efficacy outcome for the pivotal cohort. Of the 49 patients, no information was available on closure status for two patients, in one case, because an echo was not performed and was missing

and, in one case, because an echo was deemed uncertain by the core laboratory.

In the patients for whom data are available, 44 of 47 patients, or 94 percent, had documented complete closure. One patient had a less-than-1-millimeter residual defect and two patients had larger defects noted.

[Slide.]

Although the type of echocardiogram was not specified by protocol, for the purposes of this discussion, we have outlined the types of echos that were done. In the majority of cases, trans-thoracic echos were used as the primary mode of assessment.

In three-quarters of patients, the treating physician did perform a contrast injection at one point during the follow-up period.

[Slide.]

This slide now shows the complete closure rates for the STARFlex device and the two predecessor devices as outlined in the panel pack. As I said, the closure rate for the STARFlex device was 94 percent in this cohort whereas, in the CardioSEAL device, it was 80 percent and, in the Clamshell I device, it was similar.

As mentioned previously, the CardioSEAL and Clamshell device do not have this centering spring mechanism.

[Slide.]

This slide now shows the improvement in oxygen saturation in the patients for whom this was applicable. The median oxygen saturation improved from 88 prior to implant to 99 after the procedure. These results are statistically significant.

[Slide.]

This slides shows that a similar effectiveness was seen with the two predecessor devices although the median follow-up saturation was somewhat lower, probably again reflecting the higher residual leak rate with the predecessor devices.

[Slide.]

In terms of the occurrence of embolic events, the median follow-up time for the pivotal cohort is 6.5 months and, over this time period, no strokes were identified. Four patients had transient neurological symptoms.

[Slide.]

The periods of follow up are substantially longer in the two additional device cohorts.

Median follow up for the CardioSEAL device is 14 months and, in the Clamshell, device it is 56 months. This slide shows the number of strokes that were observed during the follow-up period in each of the three cohorts.

As I said previously, no strokes were observed in the pivotal STARFlex cohort. One patient in the CardioSEAL cohort experienced a stroke as did one patient in the Clamshell cohort.

[Slide.]

We were asked by the FDA to try to get a better understanding of the numbers of strokes that might have been expected in our cohorts. To do this, we present our understanding of patients risk for strokes in this particular group of patients.

The risk for stroke for an individual patient is the sum of their risk from attributes other than a PFO plus their risk from the PFO plus their risk from the procedure. Therefore, successful PFO closure should reduce the risk of stroke to the expected risk based on patient attributes.

This expected risk can be conservatively approximated as the risk in the general population matched for age and gender.

[Slide.]

To calculate the expected stroke incidence in the general population, we used two data sources. One is published data from the Framingham Heart Study, which reports information by age and gender for first-time stroke rate. We also used similar information from the American Heart Association 2002 Heart and Stroke Statistical Update. In general this information that AHA presents is derived from CDC data, and it shows first time or recurrent stroke rate by age and gender.

[Slide.]

In the pivotal cohort, we had 55 person years of follow up. In the combined PFO cohorts, 408 person years of follow up were available.

[Slide.]

Each of the person years of follow up were stratified by age and gender. The expected first-time strokes were then calculated assuming the population-based incidence rates from the Framingham study. The expected first-time were calculated assuming population-based incidence rates from AHA update.

[Slide.]

This slide summarizes the results from this comparison. The expected first-time stroke rates in the pivotal cohort was 0.064 and, in the combined cohort, was 0.90. The expected first and recurrent stroke rates were 0.73 and, in the combined cohort, was 1.35. The observed stroke rates in the pivotal cohort were 0 and in the combined cohorts were 2.

[Slide.]

It is not possible to do formal power analyses doing this analysis because of the age and gender stratification. Therefore, to show what the stroke rates would have needed to be, we, therefore, instead present the hypothetical stroke rates that would be necessary to have been observed in order to achieve statistical significance.

For the PFO pivotal cohort, if we had observed two strokes during the follow-up period, this would have been different than the stroke rate in the general population for first-time or recurrent strokes. As I mentioned previously, zero strokes were actually observed.

[Slide.]

In the combined cohorts, if we had observed five strokes, this, then, would have been

higher than the level that would have been expected in the general population matched for age and gender for first-time or recurrent strokes. As I mentioned, previously, two strokes were observed.

[Slide.]

Seven patients in the study met the primary safety outcome of having experienced at least one serious or moderately serious event that was probably or definitely related to the device implantation or catheterization procedure.

[Slide.]

This slide shows the nine events experienced by those seven patients. One patient had three events initially catheter-induced arrhythmia during the procedure, afterwards, post-procedure atrial fibrillation, then symptomatic thrombus both on the device and within the atrium as noted at device explant approximately six weeks after the procedure.

Six additional patients had one event each, one episode of catheter-induced arrhythmia, one episode of transient air embolism with no sequelae during the procedure, one retroperitoneal bleed that did not require intervention, two episodes of post-procedure vomiting requiring

medication and I.V., fluid administration and one further episode of atrial fibrillation.

[Slide.]

Once again, additional adverse events were tabulated as a secondary safety outcome and were reported in half the cohort.

[Slide.]

This slide shows the categorization of these larger number of events, the majority of which were deemed by the safety committee as being unrelated. Seven patients did have a device-arm fracture detected during the period of follow up without any clinical sequelae.

[Slide.]

This slide shows a Kaplan-Meier curve of the time to first device-related event. As you can see, the events do appear to occur quite early.

[Slide.]

This slide now shows all of the additional events that were in any way even possibly related to the device throughout the follow-up period. All are episodes of possible arrhythmia.

[Slide.]

No patients died during the follow-up period and the only device explanted is the one

that I told you about previously.

[Slide.]

This slide now shows a similar type of information from the larger CardioSEAL cohort. One patient experienced an episode of atrial fibrillation during follow up with a possible strand of thrombus noted that resolved on treatment and one patient had a malpositioned device.

[Slide.]

Once again, these events were noted relatively early after the procedure.

[Slide.]

This slide now shows similar information from the Clamshell cohort. In this cohort, two patients experienced device embolization. One had significant hypotension. One patient had a friction lesion noted in the location of a device-arm fracture. This device was ultimately explanted and one patient experienced a stroke during follow up with adherent thrombus described as superior on the atrial septum, apparently closely related to the device. This resolved on medical treatment and the device was explanted one month later. No thrombus was present at the time of device explanation. In addition to the

thrombus, this device had a residual leak which I believe was a part of the reason for going forward with explanation even though the thrombus had resolved.

This patient also had post-procedure atrial fibrillation and, six months later, was diagnosed with a lung primary.

[Slide.]

This slide now shows these device-related events in the much longer follow-up period of the Clamshell I cohort. A late event at nine years after implant is the late drop on this slide.

[Slide.]

In conclusion, in a complex group of patients at risk from PFO patency, implantation of a STARFlex device achieved complete PFO closure in 94 percent of patients, higher than predecessor devices. PFO closure resulted in significant improvement in cutaneous oxygen saturation in patients with right-to-left shunting and cyanosis.

Incidence of stroke during follow up was no different than would be expected for first or first and recurrent strokes in the general population matched for age and gender. Procedural adverse events were infrequent and manageable and

late events were rare.

Thank you very much.

I would like to introduce the next speaker, Dr. Nancy Futrell. Dr. Futrell is the Director of the Intermountain Stroke Center in Salt Lake City and she is the Chair of the Stroke Section for the American Academy of Neurology.

Concluding Remarks

DR. FUTRELL: Good morning.

[Slide.]

My name is Nancy Futrell. I have no financial interest in NMT Medical. I will be reimbursed by the company for my expenses in making this trip and for my time away from work.

[Slide.]

We are all well aware of the public-health implications of stroke. It is the number-three killer in the United States and the leading cause of disability. Clearly, a large number of the patients who suffer strokes will go on to permanent disability and the financial expenses are horrendous.

Treatment options are improving and secondary stroke prevention is clearly better than it has been in years, but there are subgroups of

stroke patients who still have inadequate secondary preventative measures available.

[Slide.]

We have known for a long time that congenital heart disease is the primary cause of stroke in patients under age 4, but, historically, patent foramenal-valley and paradoxical emboli have been considered rare events in adults. The major treatment we have offered these patients in the past has been either open-heart surgery or chronic anticoagulation which has been less desirable because of the young age of the patients and because of the complications of the open-heart surgery.

[Slide.]

Things are changing with new diagnostic techniques and we are now aware that patent foramenal valley is probably a risk factor for stroke in some number of young patients. We say here under age 65, but, clearly, many of those of us in practice are seeing this in patients in their twenties, thirties and forties.

We have improved techniques for diagnosing the patent foramenal valley which are both sensitive and specific and, further, the new

techniques allow us to get a lot more information on the anatomy of the PFO and look for the specific defects which are higher-risk defects for recurrent stroke

We know that pharmacologic failures are not infrequent. Patients go on to have recurrent stroke in spite of full antiplatelet therapy and full anticoagulant therapy. It is thought that this is, in part, from the sequestration of blood in the tunnels of the patent foramenal valley making anticoagulation less effective. These patients are a real problem to us in everyday clinical practice.

We have all been waiting for adequate percutaneous device to be available for closure in order to avoid surgery which is a major consideration in our patients.

[Slide.]

The study material that has been presented today does have some limitations and we are all well aware of those but there are some strengths in the study. First of all, there was a panel which determined the appropriateness of patients for the catheter closure and validated the need for this closure to occur.

The patients were all followed prospectively. There is a reasonable assurance of clinically meaningful benefit to these patients as they were well known to be high-risk patients many of whom had already had recurrent events on full-dose Coumadin.

The study further provides reasonable assurance of safety and efficacy. The complications were manageable and the long-term and short-term safety of device placement and of long-term device in the body has been clarified by these trials.

[Slide.]

These patients are like some of those that we wrestle with in clinical practice where they had few, if any, acceptable treatment alternatives. The patients are at high risk and would prefer, as we, as the physicians would prefer, to find a nonsurgical option.

Furthermore, because a lot of these patients are young, it is of concern to me as their physician to expose them to the cumulative risk of anticoagulation and/or antiplatelet therapy over the decades of their lives. They are difficult patients for neurologists and we were pleased, as

neurologists looking at the study, to see that this high-risk group of patients were able to have their stroke risks reduced down to that of the general population with the closure device.

[Slide.]

The indications for the use that have been proposed by the company are to close patent foramenal valley with the STARFlex device in patients who are at risk for recurrent cryptogenic stroke or transient ischemic attack when those are presumed to be caused by paradoxical embolism from the PFO. These are to be limited to patients who are poor candidates for surgery or for conventional therapy for a variety of reasons.

[Slide.]

Which patients are in practicality from my practice candidates for STARFlex closure in the future? First of all, I am looking for patients who have a history of a definite embolic neurologic event. We carefully need to rule out alternate sources of embolus, in other words, that will improve the likelihood that the patent foramenal valley is, indeed, responsible for the event.

We need to look for risks of conventional therapies and we need to determine those patients

who have higher anatomical risks of the patent foramenal valley. We know atrial septal aneurysm has been associated with higher risk when a patent foramenal valley is present.

Currently, as our understanding of the patent foramenal valley is improving and as we are looking at more of these patients with recurrent events, we are getting better understanding of the anatomy and risk of these lesions.

[Slide.]

Surgical closure is a problem. It has increased morbidity and clearly increased cost and recovery time. When we compare the types of morbidity we see in the supporting data presented today compared with the types of cognitive problems that we, as neurologists, see after patients have been on the pump, it is clear that there are some advantages to a non-surgical approach.

As far as pharmacologic therapy, there are also inherent problems here. Cumulative lifetime risks of decades of pharmacologic therapy are significant. Risk of anticoagulation alone is 1 percent per year. Pregnancy is clearly made more dangerous by antithrombotic therapies and, furthermore, we have to switch the pregnant

patients from Coumadin to heparin if they are on anticoagulant.

It is a significant expense during the pregnancy and a significant risk to the mother. Lifetime blood tests are required with many of these treatments and long-term compliance, as you know, is a problem with medical therapies.

[Slide.]

The concern is what happens in the PMA environment when we make the device more available. I believe we are all concerned for the need to control device usage, make sure it is appropriately used in only high-risk patients.

[Slide.]

Neurologists ought to be the primary gatekeeper. The majority of the patients in the study presented today were, in fact, stroke patients. The majority came through the neurologists. Clearly, there is a move nationwide in the Stop Stroke Act to see that neurologists are, in fact, managing and seeing most of the patients with strokes.

We need to define, and this includes probably in the label, itself, what those high-risk PFO groups are. Clearly, only centers with a

cooperative stroke program, an interventional cardiology program, who are working together to both select patients and assure the quality of selection and outcome should be allowed access to this device.

There will be more postmarketing study needed.

[Slide.]

There are other groups of patients who may become candidates for STARFlex closure in the future but these concepts are evolving and these patients should not be candidates for therapy until appropriate studies are done. Based on our current evidence and our clinical practice, we know that there are some high-risk stroke patients with recurrent strokes on medical therapy who are benefitting from STARFlex closure.

Further, we have seen, both in the studies and in clinical practice of the earlier-generation devices, that the STARFlex and the STARFlex predecessors are safely and completely closing patent foramenal valley and reducing the risk of recurrent stroke.

Thank you.

DR. TRACY: Thank you very much.

Are there any short clarifying questions from the panel before we move on to the FDA presentation?

DR. PINA: Dr. Tracy.

DR. TRACY: I'm sorry. Dr. Pina?

DR. PINA: In your long-term cohort with the Clamshell, how many of those patients do you actually have follow up on? I saw the rate of stroke and all that, but it has been a while, apparently, since those patients came through your institution. How many of those do you actually have follow up on today?

DR. JENKINS: There is some follow-up information in the vast majority of the cohort. The curves are presented as Kaplan-Meier curves so it would be through the period of last follow up.

DR. TRACY: Thank you.

Can we move on to the FDA presentation, please.

FDA Presentation

MS. BUCKLEY: Good morning.

[Slide.]

My name is Donna Buckley. I am a mechanical engineer in the Interventional Cardiology Devices Branch in the Office of Device

Evaluation at the FDA. I am also the lead reviewer for the CardioSEAL STARFlex septal occlusion system PMA, supplement submission P000049, Supplement 3.

Today, Dr. John Stuhlmuller and I will present the FDA summary for the STARFlex system. This device is a transcatheter septal-defect occlusion system used in the treatment of patent foramenal valley.

Your points of discussion for the clinical study results and labeling recommendations will be taken into consideration by FDA and the evaluation of the application. Finally, you will be asked to vote on the approvability of this application.

[Slide.]

The FDA summary will provide a brief overview of the FDA review team, background, device description, nonclinical evaluation, clinical evaluation and questions directed to the panel.

[Slide.]

Members of the FDA review team present today are Donna Buckley, myself, and Dr. John Stuhlmuller, the medical officer for the file from the Office of Device Evaluation and Dr. Gerry Gray from the Office of Service and Biometrics, the statistical reviewer for the application.

[Slide.]

NMT Medical received HDE approval for the CardioSEAL device for the treatment of PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed medical therapy. They also received PMA approval for the CardioSEAL device in December, 2001 for the treatment of ventricular septal defects in high-risk patients.

The STARFlex device is similar in design to the CardioSEAL device except that the STARFlex device includes a nitinol centering spring.

[Slide.]

The occluder is a double umbrella design with an MP35n metal frame, attached polyester material and a nitinol centering spring. Approval is sought for three sizes ranging from 23 to 33 millimeters and the device size to defect diameter ratio is generally 1.7 to 2.0 to 1.0.

[Slide.]

The implant is loaded into a 10 French delivery sheath using the Quik Load device. It is attached to the delivery system tracked through the delivery catheter and deployed across the defect. In vitro or bench testing, as outlined in Section

1.4 of the FDA summary, was performed the evaluate the mechanical integrity and function of the STARFlex device.

Biocompatability testing of the device components was conducted in accordance with ISO10993. Animal studies on sheep models were performed to evaluate acute one-month and three-month outcomes and the results of the bench biocompatability and animal testing demonstrate the integrity and functionality of the device for its intended us and there are no outstanding preclinical issues.

Now, Dr. Stuhlmuller would like to make a few comments about the clinical evaluation and I will come back and address the questions to the panel.

DR. STUHLMULLER: Good morning.

[Slide.]

My name is John Stuhlmuller. I am a medical officer in the Interventional Cardiology Devices Branch in the Division of Cardiovascular Devices. I am going to provide a brief overview of the clinical information contained in the PMA supplement.

[Slide.]

Clinical datasets: the sponsor has provided information for four different clinical datasets. First is the pivotal cohort for PFO closure using the STARFlex device. The non-pivotal clinical datasets include the following: use of the CardioSEAL for PFO closure, use of the Clamshell I for PFO closure, and use of the STARFlex for closure defects other than PFO.

On the pivotal cohort for PFO closure will be reviewed at this time.

[Slide.]

Pivotal cohort: the pivotal cohort for PFO closure is a retrospectively derived, open-label, single arm patient subset of the high-risk registry conducted under an IDE at Boston Children's Hospital. No control group has been identified. Patients were eligible for device placement if surgery was either technically difficult or impossible or if the patient was sufficiently sick that surgery would pose an unacceptable risk.

Enrollment in the registry is consistent with the compassionate-use criteria as outlined in the expanded-access provisions of the Food and Drug Administration Modernization Act of 1997. The registry is also primarily a single-center study.

[Slide.]

A total of 49 patients were retrospectively identified for inclusion in the pivotal cohort for PFO closure. Devices were placed in 49 of 49 patients in whom device placement was attempted.

[Slide.]

Indications for closure: indications for closure included prior neurological event in 39 patients, presence of right-to-left shunt in only seven patients, and both a prior neurological event and shunt in three patients.

[Slide.]

Patient outcome assessment, effectiveness: no prespecified outcome measures were provided for assessment of effectiveness, clinical benefit. Procedural success defined as a reduction of embolic risk using echocardiography, a surrogate endpoint, has been proposed as the primary efficacy outcome measure for assessment of clinical benefit.

Evaluation of a recurrent neurological event, a clinical endpoint, has been proposed as a secondary outcome measure for assessment of clinical benefit.

Safety: no prespecified outcome measures

were provided for assessment of safety, clinical benefit versus risk. The primary safety outcome was assessed by evaluating the number of patients who experienced serious or moderately serious device implantation- or catheterization-related adverse events.

[Slide.]

Effectiveness, echocardiographic assessment. Of the 49 patients enrolled, no echo information was available for five patients. No echo follow up was provided in two patients and echos were classified by the core lab as uncertain in three patients. Therefore, echocardiographic assessment was only completed in 44 of 49 patients.

The sponsor reports closure in 43 of 44 patients for a procedural success rate of 97.7 percent. Of the 44 patients, six patients were classified as having complete closure based on preliminary review in which the core-lab readings were uncertain. Technical imaging errors occurred in nine of the 49 patients.

No strokes and four transient neurological events were reported.

[Slide.]

Safety: patient evaluations were scheduled

at one, six, 12 and 24 months after device placement. Adverse events by time of event are reported as within two days of implant, two days to one month, one month to six months and six months to most recent follow up.

Adverse events were characterized as device-related with a separate analysis for device-arm fractures, implantation-related and catheterization-related.

[Slide.]

Serious or moderately serious adverse events were noted in 13 of 49 patients in which device placement was attempted. Seven device-related, one implantation-related and five catheter-related adverse events were noted. Device-arm fractures were noted in seven of 49 devices.

[Slide.]

Study limitations: study limitations include the following; vague patient selection criteria, no control group, no prespecified study endpoints, no prespecified success criteria and no prespecified sample size.

In summary, FDA believed that this study does not qualify as a well-controlled

investigation.

MS. BUCKLEY: FDA would now like to obtain input on the following questions.

[Slide.]

The sponsor has submitted data to support the approval of the use of the CardioSEAL STARFlex device in the following patient population: patients at risk for recurrent cryptogenic stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramenal valley and who are poor candidates for surgery or conventional drug therapy.

To support this indication, the sponsor has provided a retrospective subset analysis from a registry study sponsored by Boston Children's Hospital that includes patients with various anatomic defects who are considered high-risk for surgical closure.

The pivotal cohort is comprised of 49 patients with PFOs. Regarding efficacy, no prespecified outcome measures were provided for assessment of effectiveness and procedural success defined as reduction of embolic risk using echocardiography has been proposed as the primary efficacy outcome measure for assessment of

effectiveness.

The sponsor reports a procedural success rate of 97.7 percent. Of the 49 enrolled patients, no echo information was available for five patients and, of the remaining 44 patients, six additional patients are classified as having complete closure based on preliminary review. See Table C1A in Section 5D1 of the panel pack.

Evaluation of recurrent neurological events has been proposed as a secondary outcome measure for assessment of effectiveness. There were no strokes reported and four of 49 patients were reported to have transient neurological symptoms. See Table C2A to C3A in Section 5D1 of the panel pack.

[Slide.]

Question 1a: Please discuss the use of procedural success as the primary efficacy outcome measure for assessment of clinical benefit.

Question 1b: Please discuss the use of the occurrence of potential embolic neurological events after device placement as a secondary efficacy outcome measure for assessment of clinical benefit.

[Slide.]

Regarding safety, no prespecified outcome

measures were provided for assessment of safety. The primary safety outcome was assessed by evaluating the number of patients who experience serious or moderately serious device implantation or catheterization-related events.

Of the 49 patients evaluated over the follow-up period, thirteen patients experienced a serious or moderately serious adverse event. These events were further characterized as related to the device for seven patients or related to the implantation or catheterization procedure, six patients.

There were no patient deaths or strokes during the follow-up period. See Tables B1 to B13 in Section 5D1 of the panel pack.

[Slide.]

Question 2a: Please discuss the use of serious and moderately serious adverse events as the primary safety outcome measure for assessment of clinical benefit versus risk.

Question 2b: Please discuss whether the echocardiographic evaluation and clinical evaluation allow adequate assessment of device-related clinical events.

[Slide.]

Question 2c: Please discuss whether adequate information has been provided to allow assessment of the risk of recurrent cryptogenic stroke versus risk of device-related neurological events.

Question 2d: Please discuss whether adequate information has been provided to characterize the appropriate post-device placement antiplatelet regimen or anticoagulation regimen.

[Slide.]

Question 3: Please comment on the lack of a prespecified control group, prespecified outcome measures and prespecified sample size.

[Slide.]

If you believe that the data presented today are inadequate to support safety and effectiveness, please address the following questions.

[Slide.]

Question 4a: Please clarify if additional analyses on the current dataset could be performed to provide adequate information to support safety and effectiveness.

Question 4b: Please clarify if the collection of additional data using the current

patient selection criteria and outcome measures would be adequate to support safety and effectiveness.

[Slide.]

Question 4c: Alternatively, if you believe that a new trial is required, please address the following clinical-trial design questions.

Question i: given, our current understanding of the causal relationship of the presence of PFO in stroke, please discuss whether a randomized trial is necessary to evaluate safety and effectiveness and, if so, can a randomized trial be completed at this time and what is an appropriate control group.

[Slide.]

Question ii: Please discuss whether adequate trials can be designed with historical controls or objective performance criteria.

Question iii: Based on the type of study design proposed, please address the following issue: Please characterize the appropriate patient population for study enrollment; please discuss the appropriate primary and secondary outcome measures for evaluation of effectiveness and safety; and, as part of this discussion, please comment on the use

of clinical versus surrogate endpoints.

[Slide.]

Please discuss the appropriate duration of patient follow up. Please comment on what would be a clinically relevant sample size. Please discuss the criteria for a successful trial. Finally, please comment on whether adjunctive antithrombotic medication regimens should be left to the operator or prospectively outlined in the protocol.

[Slide.]

A summary of the physician training program has been provided in Section 5 of the panel package.

Question 5: Please discuss any improvements that could be made to this training program.

[Slide.]

One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment. Identify potential adverse events with the use of the device and explain how the product should be used to maximize benefits and minimize adverse effects.

[Slide.]

Question 6a: Please comment on the Indications for Use section as to whether it identifies the appropriate patient population for treatment with the device.

[Slide.]

Question 6b: Please comment on the Contraindications section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

[Slide.]

Question 6c: Please comment on the Warnings and Precautions Section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

[Slide.]

Question 6d: Please comment on the Operator's Instructions as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

[Slide.]

Finally, Question 6e: Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse

events.

The panel package includes the available data for the STARFlex device in the pivotal cohort. In addition, data were provided for the CardioSEAL device and for the Clamshell I follow-up study, Section 5D3 of the panel pack. It includes some follow up out to ten years.

Please discuss long-term adverse effects that may be associated with the device implantation including late thrombosis formation, the risk of endocarditis, problems with late operation and arrhythmias.

[Slide.]

Question 7: Based on the clinical data provided in the panel package, do you believe that additional follow-up data or postmarket studies are necessary to evaluate the chronic effects of the implantation of the STARFlex device. If so, how long should patients be followed and what endpoints and adverse events should be measured?

Thank you.

DR. TRACY: Any brief clarifying questions from the panel to the FDA?

DR. COMEROTA: Is that all?

MS. BUCKLEY: That's it.

DR. TRACY: I think, at this point, we are bit ahead of schedule but we will go ahead and take a fifteen-minute break at this point. Please be back at a little before quarter of.

[Break.]

Open Committee Discussion

DR. TRACY: We are going to move on to open committee discussion at this point and the sponsor is invited to the table there to ease things.

I will ask Dr. Vetrovec to open with his comments and review.

DR. VETROVEC: I will try to brief. We have a very distinguished panel that I am sure can add a lot, but it just seems to me, to summarize very quickly, we were asked to evaluate the efficacy and safety of a device that was implanted in 49 patients in a pivotal study of which a minority of the patients had oxygen desaturation as a primary indication and the majority of the patients had some defined, not well defined, but some neurological event in association with high-risk attributes that warranted device placement other than medical or surgical therapy.

Several things that I think are worth

taking into consideration are whether or not the changes in oxygen saturation that are indicated in the subgroup of patients with desaturation were associated with actual clinical improvement in the patients' functional status.

I think that category of patient otherwise is fairly easy to understand, particularly if they have an improvement in functional performance. Perhaps more concerning to me is trying to wrestle with the subgroup of patients who have had cerebrovascular events.

One of the questions that troubles me a little bit is there is no clear summary of the admitting diagnoses that constituted a neurological event. That might be worth discussing because, on the other side, are four neurological events that don't categorize a stroke and are categorized as some other noncerebral ischemic event.

Yet, it is not clear to me that they were not necessarily the same initiating event that got the patient into the study and was considered a concerning neurological event. So it would be worth comparing those, it seems to me, events and I would be interested in the sponsor's comments.

I would also wonder about the use of the

AHA stroke criteria as a "control" when there are published data as to the relative risk of stroke in patients with PFOs with various defined medical treatment and why that was not used as the comparative cohort in the presentation that we saw. I would further ask, just to be certain, that these patients only have PFOs and that they are not subgroups of patients with associated atrial septal aneurysms. That seems not to be well-defined in this.

The last comment I have is if one looks at Page 12 of the handout we have of the presentation, on there is a list of the TEE versus TTE endpoints. One of the things that strikes me, looking at this, is there are definitions of trivial residual flow or small residual flow in a group of patients that only three of whom had transesophageal echos. Yet, the vast majority of these patients had transesophageal echos pre-implantation of the device.

One of the questions would be how many of those patients pre- required either bubble studies or specifically a transesophageal echo to identify the shunt and were the same criteria able to--I mean, were there matching diagnostic studies at the

end.

That is, if a patient required a TEE, to show the shunt before implantation of the device but only had the TTE at follow up, do we really know that that is a closed defect.

So I would, I guess, ask the sponsor to comment on those issues.

DR. TRACY: For the sponsors, again, please identify yourselves.

DR. JENKINS: I am Kathy Jenkins. Let's see if I had all four of them down correctly. The first one was about whether the definitions that got you into the study were the same as the definitions that were classified as outcomes after the study. Is that your first question?

DR. VETROVEC: Correct.

DR. JENKINS: And whether, I think particularly the transient neuro-type events that were seen afterwards and recorded as potential events were the kinds of events that were seen previously. I think that is a very good question. I actually don't have quantified information for you of the numbers of strokes and numbers of recurrent events that the original cohort had prior to this.

I think it is very important to understand that the entire protocol is, in my mind, more a clinical effectiveness rather than efficacy trial, to use the precise term. The events that had occurred previously were of sufficient potential to have been embolic to have gotten the patient referred for the study.

The events that occurred subsequently were actually interpreted in light of what the people knew about the closure status and the clots on the device by the treating physicians. So I think your point is a good point and we certainly could go back and clarify that for you. But I don't have that information for you now.

The second question was a comparison of the AHA stroke data rather than the papers in the literature of cohorts of patients treated medically for stroke. This is a big issue in this study and in the choice of our presentation of the data. It is actually an even bigger issue in the more comparative PFO trials that are being contemplated.

I, personally, believe that one problem with many of these studies is that the issue of baseline patient risk versus attributable risk to the PFO has not been well defined in many of those

studies. I didn't find a comparison cohort in the literature that I felt we could control for baseline risk of patient separate from the PFO that would be an appropriate comparison.

So Kimberlee Gauvreau chose, instead, to go all the way back to sort of basics of simple age and gender distributions rather than adjusting for things that were not well presented in the literature and couldn't have been easily adjusted for in our patients in terms of understanding follow-up stroke rates.

That is our basis for our presentation of the information rather than any of the literature comparison cohorts. In the follow-up studies, patients can experience strokes even after successful PFO closure and then it gets attributed to something else. I see that as a failure of the diagnosis of the PFO in the first place and an issue of attributable risk to the PFO.

I think the next question was about the atrial septal aneurysms. We have that information and we didn't actually present it to you because of the subgroup analysis problem. We are very appreciative that these are very small cohorts that we are giving you.

In our entire PFO cohorts overall, we have, in general, observed approximately 10 percent of our population to meet a definition of atrial septal aneurysm. We have not stratified the outcomes by this 10 percent category, but they are included in all three of the cohorts.

Then the last question was about whether the PFOs had been identified by TEEs pre- and then by TEEs during follow up. I should clarify, by the way, that I think part of the decision not to use TEEs during follow up is remember that the vast majority of patients had TEEs done during the procedure with closure assessed at that point.

That is actually not an endpoint for our study. I wish, in retrospect, it had been. We actually used discharge echocardiography and then subsequent evaluations to assess closure status over time. So those information are not presented to you even though they were done.

I should also just comment about the TEE use and IVE use. As I said, this issue was specifically addressed by our safety committee at one point early in the trial. I think this is a reflection of the pediatric bias. These are pediatric centers predominantly and issues of

multiple procedures and even IVs, I think, are a more sensitive issue in the pediatric context.

But, perhaps more importantly, transthoracic views in younger patients are actually often deemed adequate. In our study, we did use this, the judgment of our clinicians regarding this. So I do think your point is well taken about the comparative nature of this, of the assessment.

DR. VETROVEC: I guess one thing that would be helpful is if you could convince us that the TTEs on the patients pre- indicated the shunt and you didn't need TEEs to show the shunt or bubble studies because only three-fourths of the patients got bubble studies and only three patients got TEEs afterwards. So there is a huge--if you needed great sensitivity pre- to show the shunt, you don't have the same sensitivity post.

DR. JENKINS: One issue just in terms of the FDA presentation of the closure-status data, we actually received the comments from the FDA after the due date for the panel submission. So I believe that you did receive a supplement which was some clarification of some of the questions that they asked.

One issue particularly was the echo-closure status. It wasn't actually technical issues related to imaging that prevented the core-laboratory assessments in the original submission. It was a recording glitch and problem that we couldn't solve quickly.

But the newest information which was presented to you in advance and summarized in my slide is 100 percent core-laboratory reviewed with the two uncertain studies that I mentioned previously.

DR. FUTRELL: If I could just add on the literature comparison and why we chose the Framingham study for comparison, if we look at what is in the literature, we had several problems in trying to compare it to the pivotal cohort. First of all, the patients in the pivotal cohort were younger than those in any of the published PFO literature.

Furthermore, these were not patients who came into the trial because of a simple PFO and one stroke, as some of the things we see with the WARSS and Mas. These were essentially simple, often one-time strokes.

But, if you look at the pivotal cohort

with n equals 49, over half of these patients, actually 33 of these patients, had severe complicating factors that can't be replicated in any of the published literature on PFO. Thirteen of these patients had complex medical and cardiac disease which would have eliminated them from much of what is in the literature.

We had complex cardiac shunt with desaturation which, again, is different than what we see in the WARSS study or the Mas study. We have failure of medical therapy either with recurrent events or complications of the medical therapy in fourteen patients.

So we essentially have a more complex patient entry group than we can find in any of the published literature so the comparison was difficult to make.

DR. TRACY: Thank you.

We actually have two lead reviewers for this application and I will ask Dr. Marler to ask questions.

DR. MARLER: So the question I have is the control group. The--I am just trying to figure out how to phrase it. Could you relate the control group and the patients that you studied to the

indication that you are requesting which isn't limited to patients with an apparently higher risk?

DR. FUTRELL: I am not sure what you are getting, at John. There was not a control group as we know. It was a single-arm trial.

DR. MARLER: Right. Who are you proposing to use the device in in the future? What is the indication you are asking for here?

DR. FUTRELL: Patients with embolic ischemic events in the brain who have absence of other risk factors leading one to conclude the PFO is a highly likely reason for that and patients who have contraindications to other therapies, medical therapies.

DR. MARLER: To me, that seems very similar to the group that is described in the WARSS PFO substudy.

DR. FUTRELL: The WARSS PFO subsets didn't have the kind of recurrent events. Obviously, if somebody has a PFO, we think the PFO is the cause, we put that patient on Coumadin. The patient has another event through Coumadin. We want to have the option to close that PFO. I don't think we had anything like that in WARSS.

DR. MARLER: So you are talking about

patients who have had two events?

DR. FUTRELL: Certainly, that is one category of patient that we see and it is not an infrequent one that we see in clinical practice of young patients with PFOs, no other stroke risk factors, and they fail Plavix and they fail Coumadin.

DR. BAILEY: How many of your pivotal group had multiple events at baseline, history of two or more?

DR. FUTRELL: At baseline, I don't know. But, clearly, the criteria for entry into the study, there were a number of those patients who had failed medical therapy so, obviously, that was a recurrent event.

DR. BAILEY: I thought I understand failed medical therapy could also mean intolerance to anticoagulation.

DR. FUTRELL: There were three patients who failed Plavix and aspirin. There were six patients with recurrent ischemic events on Coumadin. There were four patients who had side effects of Coumadin and one patient who couldn't get the Coumadin dosing right.

So six patients breaking through full

dosing anticoagulation.

DR. BAILEY: Okay.

DR. JENKINS: Although we didn't tabulate specifically the number of events that had occurred, if that is your question, what was the distribution of the number of prior events. We didn't tabulate that.

DR. MARLER: I found what I was looking for. I'm sorry, on Page 17, you are saying, "indications for use for both proposed closure of patent foramenal valley in patients at risk for a recurrent cryptogenic stroke or transient ischemic attack due to presumed paradoxical embolism through a PFO and who are poor candidates for surgical or conventional therapy."

So you were saying patients who had had a recurrent stroke.

DR. FUTRELL: Patients who have a recurrent stroke in spite of medical therapy would certainly be--and if you say poor candidate for medical therapy, if medical therapy doesn't work, I think they are a poor candidate for medical therapy. A failure of medical therapy would say that they are a poor candidate for using that as a long-term prevention.

DR. JENKINS: There are other types of patients who could meet the broader definition.

DR. MARLER: I was trying to relate, then, again, the patients that were in your study to the patients that you propose to use it in. You had said that the WARSS patients, the patient with cryptogenic stroke, the patients with PFO, would not be included in the study or would be--would be included for future use or would not?

DR. FUTRELL: No. My point about the WARSS study was that that population was a lower risk population. Even if you take just those patients who entered WARSS, were found to have PFOs, take that subgroup, those were a lower-risk PFO population than this population because this was a sicker population, more congenital heart disease, and patients who had already, in many cases, had a history of breaking through medical therapy.

Any patient who had already broken through Coumadin would not likely have been randomized to WARSS.

DR. MARLER: So my question is would not the patients who were in WARSS, who had a PFO and cryptogenic stroke, be eligible by the Indications

for Use proposed.

DR. FUTRELL: Some would, I think, but it wouldn't necessary all be. Some would. We are talking about people with more than just a PFO and a stroke. The patients in WARSS were people with a stroke, then you happened to find a PFO. So all they were is you take stroke patients across the board who have PFOs.

If you rule out those with major carotid stenoses, which were ruled out of WARSS, rule out those with absolute cardiac sources of emboli, which are ruled out of WARSS, you are taking a group of patients that entered the trial because of a clinical event and were then found to have a PFO.

That is different than what we are talking about. We are talking about the patients who had a clinical event, were then found to have a PFO but had additional problems that the WARSS patients don't have.

DR. MARLER: Okay. So I am trying to find out how that is included in your Indications for Use proposed.

DR. FUTRELL: In the slide that says which patient is a candidate for STARFlex PFO closure, my concept of who needs consideration of PFO closure

is somebody with a history of neurologic events. That is no different than WARSS.

Other sources of embolus ruled out is a little different than WARSS because we were just talking about ruling out a carotic stenosis that was significant enough for surgery. I think we need to be a little bit more detailed about that in patients with significant atherosclerosis that need systemic treatment for atherosclerosis, even if that treatment is not surgery, should not go to PFO. They should have medical treatment for their atherosclerosis. They shouldn't be going to PFO closure as the first thing.

Those with higher risk of conventional therapy, in that people who are pregnant women or women who plan to go through future pregnancies, that is a risk for conventional therapy. Those patients weren't the WARSS patients. That is completely different.

So I am saying we need much more than just what got patients into WARSS and had a PFO.

DR. MARLER: Would you agree that, in those patients who did have an event and were found to have a PFO and were followed in the WARSS study, there seems to be little relationship in the

recurrent stroke as to whether or not they did have a PFO?

DR. FUTRELL: Those are clearly the data presented in the study. But, again, there is a lot more information on the horizon about the high-risk anatomy of PFO that wasn't addressed in WARSS. So, although they did address the atrial-septal-aneurysm issue, there are more issues of size of shunt and of tunnel characteristics which may turn out to be pertinent as the tunnel is a place where a clot can be sequestered.

Those issues weren't addressed by WARSS, in part because, as you know, when we design a clinical trial, by the time the trial is finished, we have new information that, had we had more--had the TEE criteria for the high-risk PFO anatomy have been better defined at the outset of WARSS. Then we would have had more information we could put in.

So there is clearly a difference there in terms of the high-risk anatomy evaluation. The other thing that I cannot figure out about WARSS is how they can define the shunts and high amounts of shunts when they are talking about ten bubbles. When I look at their echo results, it doesn't make any sense. Their amount of traverse bubbles across

the PFO is so low, it has nothing to do with the kinds of patients that we are seeing in our clinic and the kinds of PFOs we are seeing on TEE. I can't make sense of it.

DR. KULIS: If I could just ask Dr. Michael Landzberg to come up and clarify a little bit more on the question about the WARSS study and how it relates to the proposed Indications for Use. I'm sorry; I didn't introduce myself. My name is Anne Kulis with NMT Medical.

DR. LANDZBERG: Hello. I'm Mike Landzberg. Two aspects to relate to you with regard to the questions that you have asked. Number one, these patients are different than the patients enrolled within WARSS. These, by definition, are high-risk.

DR. MARLER: Are you talking about--

DR. LANDZBERG: The patients in the pivotal study.

DR. MARLER: I understand that. I was asking--okay; go on.

DR. LANDZBERG: And the patients that are being proposed are different than the patients that were included in WARSS which was all-inclusive by definition. These, by definition, the patients

that we are proposing, are patients that are poor candidates from either a medical standpoint or from an anatomic standpoint for standards of therapy.

Similarly, the questions and the difficulties in extrapolating from WARSS to this population has to do, again, with attributable risk to the foramen, itself, versus other medical confounders. WARSS, in itself, recognized that there were statistically different medical confounders in the populations that were studied that made this a difficult-to-assess risk.

So the issues of medical confounders versus attributable risk to the foramen were never addressed by WARSS.

DR. MARLER: All right. But I still don't think you have addressed my question of how your Indications for Use proposed would exclude the patients that were in WARSS.

DR. FUTRELL: If you just take the high-risk for conventional therapy, that would exclude a lot of WARSS patients. By definition, to enter WARSS, they had to be Coumadin candidates. We are talking about a lot of patients who aren't Coumadin candidates so I think that is a big one right there.

DR. MARLER: I guess I am just not communicating my point. I am trying to figure out who you are proposing to use the device in and how clearly specified it is. To me, it looks like the Indications for Use are reasonably broad and don't--it is not clear to me how you would distinguish what you are proposing--the patients you are proposing to use it in and the patients, for instance, that were in WARSS among many others.

DR. BECKER: Anne Kulis, again. I would like to ask Dr. Likosky to come up and provide a little bit more insight on this issue, please.

DR. LIKOSKY: I am Bill Likosky. I am Director of the Stroke Program at Swedish Hospital in Seattle. I don't have any financial interest in the company. They are paying my expenses and time for coming.

I think, to some degree, from a neurologist's perspective, we have patients who are relatively young when they have stroke in which there appears to be no other etiology which would easily explain it.

At the same time, we have some patients who, by the nature of their PFO, look as if that is the cause of it; for example, people with a large

PFO. We are currently doing bubble studies where we would quantitate passage across the PFO, people with atrial septal aneurysms and, I think, increasingly, people we recognize who have clotting abnormalities.

I think, when we look, then, at somebody who has had a presumed embolic event, and we add these other features together, we begin to define a population that could be considered people at high risk of a recurrent embolic event associated with a PFO which appears to be the culprit.

I think that, in a way, distinguishes these people from the WARSS study.

DR. MARLER: Right.

DR. TRACY: Dr. Marler, any other questions?

DR. MARLER: Not right now. Thank you.

DR. TRACY: Do you want to ask a question now or--

DR. PINA: No; I would like to ask a question in follow up to this. When you say that the patients have cardiac abnormalities, what cardiac abnormalities are you talking about? Let me refer specifically to your Page 17 where you have pulmonary vascular resistance as the reason

for the cardiac abnormalities, 16 percent.

In my experience, and you do have several cardiomyopathies in here--I counted that 26 of your patients were over the age of 30--

DR. TRACY: I'm sorry; Dr. Pina, could you tell us what page you are referring to?

DR. PINA: Page 17 under Section 5C. The pulmonary vascular resistance increase causes an otherwise closed foramenal valley to open and it is sort of a fail-safe mechanism. Actually, closing that foramenal valley causes right-sided failure.

In the packet, and I don't remember in which of your studies, you actually have a patient who developed more hepatic congestion and hepatic encephalopathy where closure of the PFO was not the thing to do because of right-sided problems.

So your patient selection and the cardiac disease, I have issues with. You also have some patients in here who have tachyarrhythmias. The tachyarrhythmias alone could be a harbinger of emboli. It doesn't necessarily have to be associated with a PFO. So, again, in your patient-selection criteria, I am having a problem with the cardiac disease without some really good delineation of what that is.

DR. JENKINS: It is actually very difficult to tabulate in sufficient detail what this cohort looked like for you. This is, by definition, a diverse group of patients. For example, the right-to-left shunting patients had congenital heart disease in the majority of cases. So I think that we have tried to just use simple categories to describe it to you. I think we have struggled to try to give you a sense of what the patient cohort looked like.

I am not sure I understand, though, how that is a criticism of our evaluation of the effectiveness or safety of PFO closure.

DR. PINA: It does have to do with patient selection. Blase, I'm sorry.

DR. CARABELLO: If I could follow up. This was a question that George asked as well. You had ten patients with right-to-left shunts and closed the hole, and, obviously, their oxygenation got better. What happened to their right-sided hemodynamics. There is always the concern that if you take the shunt flow, add it to total right-sided output, the pulmonary pressure will go up. So we surely must have data on right-atrial pressure and pulmonary-artery pressures.

DR. JENKINS: We have a lot more data about the cohort than is presented to you here. Interestingly, that particular group of patients has been a focus of discussion in the study overall, more in the ASD anatomy, rather than the PFO anatomy group. So it is really not well summarized for you here.

We did have an occasional patient who died in the study overall within a week or two after closure of an atrial septal defect, presumably due to those types of changes. Interestingly, there is actually a special category that our safety committee added partway through the study to distinguish those patients who were, perhaps, poor candidates for atrial septal closure in the study overall.

None of the patients in the pivotal cohort had that definition applied to them on review by the safety committee.

DR. CARABELLO: Right. But what I am asking is, of those ten patients with a right-to-left shunt in whom you closed it, what happened to their pulmonary-artery pressure?

DR. JENKINS: I don't have PA pressure for you. I have clinical data for you that show that

the patients did well for the follow-up period afterwards with a complete screening for adverse clinical events that would have occurred should they have compromised from that in a context where other patients had that and were reviewed and were not deemed to have had those clinical events.

DR. LAZAR: I would like to go back to Dr. Marler's notion about for whom this is indicated. Going to the notion of risk for a recurrent cryptogenic stroke, if a patient has a PFO and is found to have, or have had, a cryptogenic stroke there is no evidence, let's say, for peripheral vascular disease or other risk factors for something outside of the brain to cause a stroke or the carotid disease and so it remains cryptogenic, how do you conclude that the PFO was important, or the closure of the PFO important, in preventing another stroke if you haven't established what the stroke mechanism is in the first place?

DR. FUTRELL: Obviously, the whole business of cerebral embolism is a tricky one because our evidence is always indirect. When we are talking, even when we see a carotid stenosis, whether that is embolizing, that is indirect. When we see atrial fibrillation, that is indirect

evidence.

We know that we take a person who has had an embolic stroke. We look for all those sources that could produce emboli and we go from there. I am certainly not proposing, for any of my patients, that a person who has a single stroke and has a PFO and absolutely nothing else be put in a group that will have a STARFlex closure of their PFO.

I am looking for more than that. If I see somebody who has absolutely nothing else, comes in with a definite clinical event, has a 2-centimeter stroke on MRI to match the clinical event, often we will see one or two other silent things that we didn't recognize.

If I see a high-risk anatomy on transesophageal echo, then I would consider that person for PFO closure. So, if there is an atrial septal aneurysm and a long tunnel and I see a large amount of shunting on the transcranial Doppler with bubble study, or on the transesophageal echo, that patient would be considered.

The similar patient that has just a standard PFO, not a big atrial septal aneurysm and sort of a medium-sized amount of shunting, those patients are put on medical therapy in my clinic

and they would be considered for a STARFlex only if they failed the medical therapy.

DR. TRACY: Could I just ask that panel--let's just go around like this so that we make sure that everybody is getting a chance here. Since we are going in that direction, Dr. Zivin.

DR. ZIVIN: I have a series of questions I would like to ask. Just as a starting point with Dr. Futrell, she listed a whole series of criteria that she would, personally, like to see for patients to qualify for in order to order this device. Unfortunately, the protocol doesn't have any specifications and, as far as I can tell, approximately 20 percent of the people sitting in this room have PFOs with right-to-left shunt.

Consequently, it would be entirely legitimate for somebody to set up a TEE device in the middle of the room and have us wander by and approximately 20 percent of us would be eligible for a procedure with no indications. So it seems to me that the lack of selection criteria is critically important considering the fact that millions, if not many more, would be potentially subject to a procedure.

The second thing is that there are no

clear indications, as far as I could tell, for surgical failure. We have indications for medical failure but not for surgical failure. We have no test as to whether determining--probably the most important one is no test to determine whether closure of the PFO improves the patient outcomes.

You didn't test for that and, in medical therapies, we must prove efficacy which does not appear to have been the case here. I would like to know why it is that this device does not need to pass that standard.

DR. FUTRELL: Obviously, to address your first point, the high numbers are of concern to all of us. The high numbers of PFO individuals--we shouldn't call 20 percent of the people in this room patients--but the high numbers of PFO individuals tell us this is a common occurrence. Obviously, everyone who has a PFO is not having symptoms from the PFO. In fact, most people who have PFOs are probably not having any symptoms at all relative to those PFOs.

When we look at the bubble studies that we do in our clinic, we are finding numbers of our patients, closer to 55 percent, who have PFOs who we find right-to-left shunts on the transcranial

Doppler with agitated saline. That is what would be expected for a clinic that is basically a stroke clinic. Our population is going to be skewed to a higher number of PFOs.

But when we look at the studies we do, about one-third of those patients have higher levels of shunting and shunting at rest rather than just with maneuvers. So, if we take the PFOs, we can clearly break them into groups where a lot of them have really trivial shunting. The ones with trivial shunts can easily be moved out.

DR. ZIVIN: Did you test whether there was a difference?

DR. FUTRELL: Did I test in the trial?

DR. ZIVIN: Yes.

DR. FUTRELL: The trial didn't test the difference in--

DR. ZIVIN: Has anybody tested whether that was a difference?

DR. FUTRELL: The Mas trial did have a little something. They had mention of the amount of shunting.

DR. ZIVIN: Did they statistically prove a difference?.

DR. FUTRELL: No.